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Insulin Clearance and the Incidence of Type 2 Diabetes in Hispanics and African Americans

The IRAS Family Study

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OBJECTIVE—We aimed to identify factors that are independently associated with the metabolic clearance rate of insulin (MCRI) and to examine the association of MCRI with incident type 2 diabetes in nondiabetic Hispanics and African Americans.

RESEARCH DESIGN AND METHODS—We investigated 1,116 participants in the Insulin Resistance Atherosclerosis Study (IRAS) Family Study with baseline examinations from 2000 to 2002 and follow-up examinations from 2005 to 2006. Insulin sensitivity (S_I), acute insulin response (AIR), and MCRI were determined at baseline from frequently sampled intravenous glucose tolerance tests. MCRI was calculated as the ratio of the insulin dose over the incremental area under the curve of insulin. Incident diabetes was defined as fasting glucose ≥ 126 mg/dL or antidiabetic medication use by self-report.

RESULTS—We observed that S_I and HDL cholesterol were independent positive correlates of MCRI, whereas fasting insulin, fasting glucose, subcutaneous adipose tissue, visceral adipose tissue, and AIR were independent negative correlates (all $P < 0.05$) at baseline. After 5 years of follow-up, 71 (6.4%) participants developed type 2 diabetes. Lower MCRI was associated with a higher risk of incident diabetes after adjusting for demographics, lifestyle factors, HDL cholesterol, indexes of obesity and adiposity, and insulin secretion (odds ratio 2.01 [95% CI 1.30–3.10], $P = 0.0064$, per one-SD decrease in \log_e -transformed MCRI).

CONCLUSIONS—Our data showed that lower MCRI predicts the incidence of type 2 diabetes.

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Insulin clearance is an integral component of insulin metabolism, as it regulates the cellular response to the hormone by decreasing insulin availability and mediates certain aspects of insulin

action (1). The liver is the primary site of insulin clearance. Approximately 80% of endogenous insulin is removed by the liver, and the remainder is cleared by the kidneys and muscles (2). Clearance rates

for insulin decrease in glucose intolerance (3), obesity (4), in particular abdominal obesity (5), hypertension (6), hepatic cirrhosis (7), and nonalcoholic fatty liver disease (8).

Although the plasma concentration of insulin is largely determined by its rate of secretion and clearance, existing evidence suggests that increased insulin resistance is associated with reduced insulin clearance (9–12). Reduced insulin clearance has important physiological functions; for example, animal models have shown that decreased insulin clearance serves as a compensatory mechanism to preserve β -cell function and to maintain peripheral insulin levels in the states of insulin resistance (13,14). In addition, insulin clearance has been found to be a highly heritable trait in Mexican Americans, and specific haplotypes in the *AMPD1* gene were associated with variation in insulin clearance (15).

Despite its potential role in the etiology of diabetes, little is known about the factors that are independently associated with decreased insulin clearance. In addition, no previous study has investigated whether decreased insulin clearance predicts the risk of type 2 diabetes. In this study, we aimed to identify demographic and metabolic factors that are independently associated with the metabolic clearance rate of insulin (MCRI), and to examine its association with the 5-year risk of incident type 2 diabetes, using the data from a large, well-characterized cohort of Hispanics and African Americans with direct measurements of insulin metabolism (secretion, sensitivity, and clearance) and adipose tissue (visceral and subcutaneous) in the Insulin Resistance Atherosclerosis Study (IRAS) Family Study.

RESEARCH DESIGN AND METHODS

The study population consisted of participants in the IRAS Family Study, a family-based study designed to explore how genetics contribute to visceral adiposity and insulin resistance

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among Hispanics and African Americans. In 2000–2002, large families were recruited at study centers in San Antonio, Texas (Hispanics), San Luis Valley, Colorado (Hispanics), and Los Angeles, California (African Americans), with probands identified from the parent study (IRAS) and the general population. Recruitment was based on family size, rather than disease status (16). Of the 1,856 participants who attended baseline examinations, 1,427 (77%) returned for the 5-year follow-up between 2005 and 2006. Participants who did not return for follow-up were more likely to be male and had slightly lower levels of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) and higher values for the insulin sensitivity index (S_I) (17). The institutional review boards approved the study protocol, and all participants provided written informed consent.

Participants provided a fasting blood draw at each examination. Plasma insulin was measured by dextran-charcoal radioimmunoassay (18). Plasma glucose was determined on an autoanalyzer using the glucose oxidase method. Prevalent diabetes at baseline and incident diabetes at follow-up were defined as fasting glucose ≥ 126 mg/dL or use of antidiabetic medications by self-report. Impaired fasting glucose was defined as fasting plasma glucose between 100 and 126 mg/dL. Lipids, including triglycerides (TGs) and HDL cholesterol, were measured using standardized laboratory procedures (17). Alanine transaminase (ALT) and γ -glutamyl transferase (GGT) were determined by enzymatic colorimetric assays (19).

Abdominal fat mass was measured by computed tomography using a standardized protocol at each clinical center. The computed tomography scans were read centrally at the Department of Radiology Bio-Imaging Research Laboratory of the University of Colorado Health Sciences Center. Images obtained at the L4/L5 vertebral regions were used to determine SAT and VAT. Bowel fat was subtracted from the measurements of VAT (20,21).

Insulin sensitivity was determined using a frequently sampled intravenous glucose tolerance test (FSIGTT), with two modifications to the original protocol (22). First, insulin, instead of tolbutamide, was injected to ensure adequate levels of plasma insulin for accurate calculation of insulin sensitivity across a broad range of glucose tolerance (23). Second, a reduced sampling protocol, using 12 instead of 30 samples, was used

because of the large number of participants (24). Insulin sensitivity, expressed as S_I , was calculated using minimal model analysis (25). Insulin secretion was measured by acute insulin response (AIR), defined as the average increase in plasma insulin above the basal level in the first 8 min after infusing glucose (17). MCRI was calculated as the ratio of the insulin dose over the incremental area under the curve of insulin from 20 min to infinity (26) using the following equation:

$$\text{Clearance (L/min)} = \frac{\text{Dose} \times 1000}{\int_{t=20}^{\infty} (\text{Ins}(t) - \text{Ins}(0))}$$

where Dose is the amount of insulin injected at 20 min, $\text{Ins}(t)$ is the plasma insulin concentration in standard units ($\mu\text{U/mL}$) at each FSIGTT sampling point, and $\text{Ins}(0)$ is the fasting plasma insulin concentration determined prior to the FSIGTT glucose injection.

Demographic data (e.g., age, sex, and ethnicity) and lifestyle factors (e.g., smoking and alcohol consumption) were collected on standardized questionnaires by self-report (16). Anthropometric (e.g., height, weight, and waist circumference) and blood pressure (BP) measurements were taken according to standardized procedures (16). Duplicate measurements were made and averages were used in the analyses.

Statistical analyses

We described the characteristics of participants at baseline, stratified by thirds of the distribution of MCRI, using medians and interquartile ranges for continuous variables and percentages for categorical variables. We used generalized estimating equations (GEE1) to test for differences in continuous and categorical variables across thirds of the MCRI, adjusting for correlations within families.

Because of the skewed distribution, we \log_e transformed MCRI and modeled it as a continuous outcome. To minimize the influence of the outlying observations in variables with skewed distributions, we \log_e transformed fasting insulin, S_I+1 , GGT, ALT, and TGs and used a signed square root transformation for AIR. We used GEE1 linear regression to describe the bivariate relationship of MCRI with metabolic and anthropometric variables, accounting for age, sex, and ethnicity. We also used a multivariable GEE1 linear regression to investigate the associations

between potential determinants and MCRI. All continuous variables in the GEE1 linear regressions were standardized to a mean of 0 and an SD of 1. BMI is removed from the multivariable GEE1 linear regression because it is highly correlated with SAT.

We used GEE1 logistic regression in a multistage approach to explore the association between \log_e -transformed MCRI as the continuous exposure variable and incident diabetes ascertained in the 5-year follow-up examination. Odds ratios (ORs) per one-SD decrease in $\ln(\text{MCRI})$ were used to estimate relative risk and were presented with 95% CIs. We included covariates in the analyses if they were of a priori clinical relevance or if they were significantly associated with $\ln(\text{MCRI})$ in multivariable analyses shown in Table 3. Covariates included age, sex, ethnicity, smoking, alcohol consumption, HDL cholesterol, SAT, VAT, and AIR. We did not account for fasting insulin and fasting glucose to avoid overadjustment because these variables are determined largely by insulin metabolism, and they are on the causal pathway for the development of type 2 diabetes. We did not adjust for S_I because of its high correlation with MCRI. However, in sensitivity analysis, we additionally included S_I in multivariable regression models to determine if the MCRI-diabetes association was mediated by a reduction in insulin sensitivity. We tested for effect modification between MCRI and sex, ethnicity, AIR, S_I , VAT, and BMI on incident diabetes. A P value <0.05 suggested a significant interaction. All the statistical analyses were performed using SAS version 9.2 (SAS institute, Cary, NC).

RESULTS—After excluding individuals with prevalent diabetes at baseline, and those without measurements of MCRI, the present analysis included 1,116 individuals who attended both baseline and follow-up examinations. Characteristics of the study population by thirds of MCRI distribution at baseline are shown in Table 1. Participants had an average age of 40 years and 61% were women and 30% were African Americans. In the 5-year follow-up examinations, 71 participants (6.4%) developed diabetes. Participants with MCRI levels in the bottom third of the baseline distribution were older and were more likely to be African American. They had significantly higher values for BMI, waist circumference, VAT, SAT, fasting insulin, AIR, GGT, ALT, systolic BP,

Table 1—Characteristics of nondiabetic participants in the IRAS Family Study stratified by thirds of the distribution of MCRI at baseline (n = 1,116)*

	Thirds of MCRI distribution			P value**
	1	2	3	
n (%)	372	372	372	
MCRI (L/min)	3.1 (2.5–3.5)	4.9 (4.4–5.3)	7.3 (6.6–8.6)	
Age (years)	41.3 (31.9–49.9)	38.6 (30.1–49.1)	37.9 (29.2–46.7)	0.0047
Sex (% female)	57.5	62.6	62.1	0.3877
Ethnicity (%)				
Hispanic American	64.5	64.3	80.1	0.0051
African American	35.5	35.7	19.9	
Smoking (%)				
Never	63.2	62.1	52.1	
Former	22.6	17.2	15.9	0.0022
Current	14.2	20.7	32.0	
Use of alcohol (%)	55.2	59.9	70.4	<0.0001
BMI (kg/m ²)	33.0 (29.3–37.1)	27.9 (25.2–30.5)	24.2 (21.7–26.4)	<0.0001
Waist circumference (cm)	99.4 (92.9–107.6)	87.7 (79.1–94.8)	77.5 (71.8–85.4)	<0.0001
VAT (cm ²)	132.4 (95.8–169.2)	83.7 (56.1–121.3)	59.9 (39.1–92.3)	<0.0001
SAT (cm ²)	427.7 (312.5–573.4)	307.4 (231.8–418.5)	224.5 (154.3–305.2)	<0.0001
Fasting insulin (pmol/L)	145.8 (111.1–187.5)	83.3 (62.5–104.2)	48.6 (34.7–69.5)	<0.0001
Fasting glucose (mmol/L)	5.4 (5.0–5.8)	5.1 (4.9–5.5)	5.0 (4.7–5.3)	<0.0001
S ₁ (× 10 ⁴ /min/μU/mL)	0.7 (0.4–1.0)	1.6 (1.2–2.2)	3.1 (2.2–4.3)	<0.0001
AIR (pmol/mL/min)	950.4 (517.9–1,575.0)	660.5 (405.9–1,001.4)	456.8 (285.0–692.9)	<0.0001
GGT (IU/L)	33.0 (25.5–47.0)	26.0 (19.5–37.5)	23.0 (18.5–32.0)	<0.0001
ALT (IU/L)	9.0 (6.5–14.0)	7.5 (5.5–10.0)	7.3 (5.0–11.0)	<0.0001
Systolic BP (mmHg)	117.5 (110.0–128.0)	113.0 (104.0–124.0)	109.0 (103.0–118.0)	<0.0001
HDL cholesterol (mg/dL)	38.9 (34.0–44.1)	43.3 (38.0–50.3)	47.7 (41.5–55.6)	<0.0001
TGs (mmol/L)	1.3 (1.0–1.8)	1.1 (0.8–1.6)	0.9 (0.7–1.2)	<0.0001
IFG at baseline (%)	35.8	23.1	10.2	<0.0001
Diabetes at follow-up (%)	11.0	5.1	3.0	0.0001

IFG, impaired fasting glucose. *Data presented are medians (interquartile ranges) or percentages. **P values are calculated from GEE1 models to account for family structure, using continuous log-transformed MCRI.

and TGs, but lower values for S₁ and HDL cholesterol.

As shown in Table 2, after adjusting for age, sex, and ethnicity, MCRI showed a positive association with S₁ ($\beta = 0.3726$, $P < 0.0001$) and an inverse association with fasting insulin ($\beta = -0.3213$, $P < 0.0001$). MCRI was inversely associated with all indexes of adiposity, including BMI, VAT, and SAT ($\beta = -0.2944$, -0.3171 , and -0.2982 , respectively, all $P < 0.0001$). In addition, higher levels of liver enzymes, including GGT and ALT, were associated with reduced MCRI ($\beta = -0.1411$ and -0.1214 , respectively, both $P < 0.0001$). MCRI was positively associated with HDL cholesterol ($\beta = 0.2014$, $P < 0.0001$) but negatively associated with TGs ($\beta = -0.3479$, $P < 0.0001$). Other significant inverse associations with MCRI included AIR ($\beta = -0.1847$), fasting glucose ($\beta = -0.1835$), systolic BP ($\beta = -0.1206$), non-drinker ($\beta = -0.1128$), and nonsmoker

($\beta = -0.1521$). S₁ and HDL cholesterol were significant, independent, positive correlates of MCRI, whereas VAT, SAT, fasting insulin, fasting glucose, and AIR were significant, independent, negative correlates (Table 3).

In GEE1 multivariable logistic regression analyses, each one-SD decrease of ln (MCRI) was associated with a higher risk of incident diabetes after adjusting for demographics, lifestyle factors, and HDL cholesterol (OR 1.83 [95% CI 1.38–2.42], $P = 0.0010$). Adjusting for VAT and SAT attenuated the association to nonsignificance (1.20 [0.84–1.70]). However, the association was strengthened and became statistically significant after additional adjustment of AIR (2.01 [1.30–3.10], $P = 0.0064$) (Fig. 1).

There was no significant interaction between MCRI and sex, ethnicity, or AIR on incident diabetes. However, we observed a significant interaction of MCRI with VAT on incident diabetes.

Stratified analyses suggested a stronger inverse association of MCRI with incident type 2 diabetes in individuals with lower VAT (data not shown). In sensitivity analyses to evaluate potential mediation of this association by insulin sensitivity, the inverse association between MCRI and incident diabetes was attenuated to nonsignificance when S₁ was additionally included in the multivariable regression models (OR 1.33 [95% CI 0.80–2.22] per one-SD decrease in log_e-transformed MCRI).

CONCLUSIONS—In this multiethnic cohort of the IRAS Family Study, we identified that decreased insulin clearance was independently associated with elevated plasma concentrations of fasting insulin and fasting glucose, higher values of AIR, SAT, and VAT, and decreased levels of HDL cholesterol and S₁. Our finding of an independent inverse association of insulin clearance with overall and

Table 2—Bivariate determinants of ln(MCRI) in the IRAS Family Study, adjusted for age, sex, and ethnicity

	Estimate*	SE	P value
Smoking			
Never	−0.1521	0.0409	0.0021
Former	−0.1396	0.0519	
Alcohol (nondrinker)	−0.1128	0.0275	<0.0001
BMI	−0.2944	0.0139	<0.0001
VAT	−0.3171	0.0154	<0.0001
SAT	−0.2982	0.0145	<0.0001
Fasting insulin#	−0.3213	0.0187	<0.0001
Fasting glucose	−0.1835	0.0137	<0.0001
S _I #	0.3726	0.0117	<0.0001
AIR^	−0.1847	0.0152	<0.0001
GGT#	−0.1411	0.0164	<0.0001
ALT#	−0.1214	0.0167	<0.0001
Systolic BP	−0.1206	0.0161	<0.0001
HDL cholesterol	0.2014	0.0155	<0.0001
TGs#	−0.1670	0.0146	<0.0001

*All continuous variables are standardized to a mean of 0 and SD of 1. #Natural log transformation. ^Signed square root transformation.

visceral adiposity, as indicated by higher values of SAT and VAT, is consistent with previous findings that hepatic clearance of insulin is decreased in obese individuals (4,27–29). Compared with subcutaneous fat, visceral fat exerts a greater influence in the impairment of insulin clearance (5). These previous studies used BMI and waist-to-hip ratio as surrogate measures of obesity and visceral adiposity; whereas our study measured

body fat distribution using more detailed procedures. Our findings extend the current literature that states that directly measured visceral and subcutaneous adiposities are independently associated with MCRI.

Elevated circulating and hepatic free fatty acids (FFAs) from increased FFA flux due to obesity, in particular visceral obesity, may partially account for impaired insulin clearance (30,31). In dogs, the

elevation of hepatic FFAs, a characteristic of adiposity, results in peripheral hyperinsulinemia with a corresponding decline in insulin clearance (32). In humans, a hyperglycemic clamp study demonstrated that hyperinsulinemia caused by elevated plasma FFAs was attributed primarily to a significant decrease in insulin clearance (33). FFAs may also provide a link between the positive association that we observed between HDL cholesterol and insulin clearance. PPAR- γ is expressed primarily in adipose tissues and is implicated in HDL cholesterol metabolism through its regulatory role in the reverse cholesterol transport pathway (34). The Pro12Ala polymorphism of the PPAR- γ gene is associated with increased insulin clearance and decreased insulin-suppressed FFA concentrations, suggesting that carriers of the Ala allele are able to suppress lipolysis more efficiently (35).

Insulin sensitivity, insulin secretion, and insulin clearance are dynamic physiological processes for maintaining glucose homeostasis. The current study shows that insulin resistance (indicated by increased fasting insulin and decreased direct measures of S_I) and insulin hypersecretion (expressed as increased AIR) are independently associated with decreased insulin clearance. In addition, hyperinsulinemic-euglycemic clamp studies demonstrated that insulin clearance and insulin secretion are independent determinants of fasting insulin in individuals with or without type 2 diabetes (36,37). Decreased insulin clearance and increased insulin secretion may represent a compensatory response to obesity-induced insulin resistance for maintaining glucose tolerance. In a longitudinal study, dogs fed a fat-enriched diet for 12 weeks developed a sustained decrease in insulin sensitivity. This was followed by a transient increase in AIR and a sustained decrease in insulin clearance to maintain glucose levels in the normal range; therefore, decreased insulin clearance may serve to preserve β -cell function in insulin resistance states (13). However, we observed that elevated fasting glucose was independently associated with decreased insulin clearance. The previous study (13) in dogs modified the short-term dietary fat intake to induce adiposity so as to evaluate the concurrent compensation for insulin resistance. No change in glucose level was noted at the end of the 12-week experiment. Of note is that these lean dogs had normal insulin sensitivity before the experimental protocol to

Table 3—Multivariable determinants of ln(MCRI) in the IRAS Family Study

	Estimate*	SE	P value
Age	0.0028	0.0097	0.2638
Sex (male)	0.0053	0.0189	0.0966
Ethnicity (Hispanic)	0.0329	0.0226	0.0889
Smoking			
Never	−0.0223	0.0197	0.2114
Former	0.0087	0.0223	
Alcohol (nondrinker)	−0.0081	0.0174	0.4372
VAT	−0.0315	0.0126	0.0006
SAT	−0.0065	0.0172	<0.0001
Fasting insulin#	−0.1172	0.0155	<0.0001
Fasting glucose	−0.0201	0.0102	0.0330
S _I #	0.1947	0.0149	<0.0001
AIR^	−0.0724	0.0090	<0.0001
GGT#	−0.0134	0.0093	0.1461
ALT#	0.0021	0.0096	0.8456
Systolic BP	0.0123	0.0083	0.2211
HDL cholesterol	0.0239	0.0081	0.0056
TGs#	0.0051	0.0089	0.5232

BMI is removed from this analysis because of high collinearity with SAT. *All continuous variables are standardized to a mean of 0 and SD of 1. #Natural log transformation. ^Signed square root transformation.

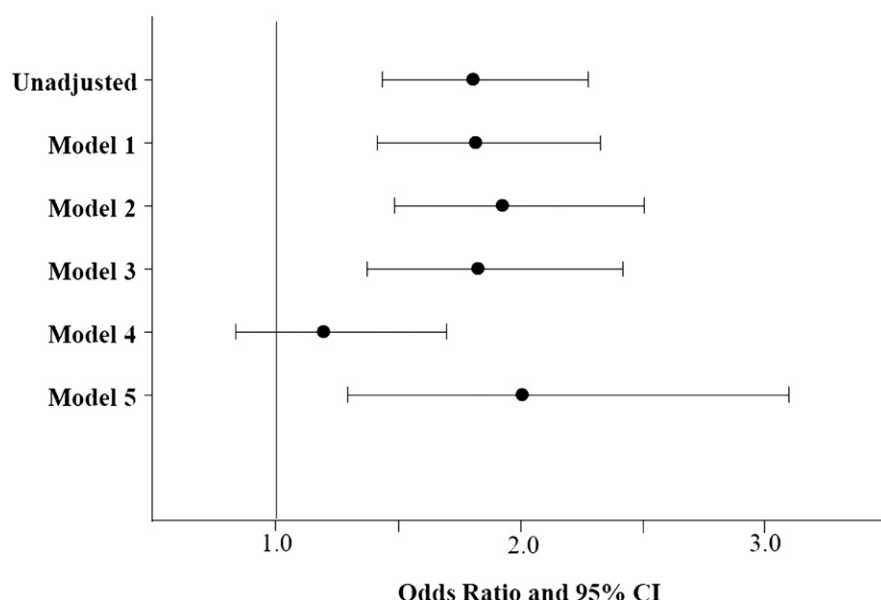


Figure 1—Association of MCRI with incident type 2 diabetes for each one-SD decrease in log-transformed MCRI at baseline in the IRAS Family Study. Model 1, adjusted for age, sex, and ethnicity; model 2, model 1 + smoking and alcohol consumption; model 3, model 2 + HDL cholesterol; model 4, model 3 + SAT and VAT; model 5, model 4 + AIR (signed square root transformation).

induce insulin resistance; hence, the results represented an early development of insulin resistance. As insulin resistance progresses, fasting glucose is expected to increase to reflect the deterioration of the insulin compensatory response. Therefore, the difference in findings between our study and the previous study (13) could be related to the time frame and severity of insulin resistance.

Ethnic differences exist in the mechanisms of adaptation to insulin resistance. African American adults and children, compared with their Hispanic and Caucasian counterparts, have lower insulin clearance and greater AIR as a consequence of decreased insulin sensitivity (38,39). These observations may stem from the differences in obesity-related phenotypes between these ethnic groups, such as accumulation of fat depots and level of insulin-like growth factor-1 (40). We observed that African Americans have lower values of MCRI than Hispanics; however, ethnicity was not independently associated with MCRI in the multivariable regression models.

In a prospective analysis, we showed that decreased MCRI at baseline was associated with incident diabetes after adjusting for demographics, lifestyle factors, and HDL cholesterol. Additional adjustment for SAT and VAT attenuated the association to nonsignificance.

However, we observed an apparent inverse association between MCRI and incident diabetes after further adjusting for AIR. We also observed a stronger inverse association of MCRI with incident diabetes in individuals with less VAT. To our knowledge, no previous study has shown these associations. The strong inverse relationship of obesity and visceral adiposity with MCRI, as discussed earlier, provides a basis for the confounding effect of SAT and VAT on the association between MCRI and incident diabetes. We have previously reported in this cohort a significant inverse association of SAT and VAT with S_1 and AIR (20), which in turn increased the risk of incident diabetes (17).

Since S_1 is highly correlated with MCRI, we did not adjust for insulin sensitivity in the main models due to multicollinearity. However, it is not surprising to observe that additionally adjusting for S_1 attenuated the MCRI-diabetes association to nonsignificance in sensitivity analyses due to their close relationships. This finding suggests that S_1 may, in part, mediate the link between MCRI and diabetes.

Including AIR in the multivariable regression models to investigate the association between MCRI and incident diabetes may represent an overadjustment as derangement of these traits are pathophysiological mechanisms on the causal

pathway of type 2 diabetes. However, adjusting for AIR could help to elucidate whether MCRI predicts incident diabetes independent of it. Of note is that our data on MCRI and AIR were determined at one particular point in time, which may not be sufficient to illustrate the complex interplay of these metabolic traits in a cohort of individuals with different stages of insulin resistance and compensatory mechanisms in the time course of their associated metabolic changes. Our observations highlight the need for longitudinal studies in humans to illustrate the progression of insulin resistance and its corresponding physiological responses.

The particular strengths of the IRAS Family Study include the well-characterized prospective cohort of Hispanics and African Americans, two ethnic groups that are at high risk of developing diabetes, and its detailed measurements of insulin sensitivity, insulin secretion, insulin clearance, and adiposity. Nevertheless, several potential limitations should also be considered. Without oral glucose tolerance tests, some individuals with elevated postprandial glucose levels may have been misclassified as not having diabetes. Finally, results of this study may not be generalizable to other populations. Our findings have important clinical implications. We observed that VAT, SAT, and HDL cholesterol are independently associated with MCRI. Since adiposity and lipids are modifiable, lifestyle modification and weight reduction should continue to be emphasized. In addition, these results support MCRI as a potential therapeutic target in preventing diabetes.

In conclusion, in this multiethnic cohort of Hispanic and African American adults, factors that are independently associated with decreased insulin clearance include elevated fasting insulin, fasting glucose, AIR, SAT, and VAT, as well as decreased HDL cholesterol and S_1 . In addition, we demonstrated that lower insulin clearance predicted the development of type 2 diabetes, independent of demographics, lifestyle factors, HDL cholesterol, indexes of overall and visceral adiposity, and insulin secretion.

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C.C.L. wrote, reviewed, and edited the manuscript and contributed to discussion. S.M.H. and L.E.W. researched data, reviewed and edited the manuscript, and contributed to discussion. C.L., J.M.N., R.N.B., D.S., A.M.A., J.I.R., M.O.G., and A.J.H. reviewed and edited the manuscript and contributed to discussion. A.J.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2010.

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